Review of 2019 Butte Study - *"Meconium identifies high levels of metals in newborns from a mining community in the U.S."*

McDermott, et al

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Dr. Charles Partridge, USEPA Region 8 Toxicologist
Nikia Greene, USEPA Region 8 Remedial Project Manager
Lynn Woodbury, CDM Smith, Denver CO

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EPA's Commitment to Butte

- ***The U.S. Environmental Protection Agency (EPA) will review all new information concerning health or environmental studies which may affect public health***

- ***EPA will work with our federal, state, and local partners to review the McDermott et al. (2019) study to determine if further studies are necessary to protect human health and the environment in the Butte community***

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Why is EPA reviewing the data from the McDermott study?

- Scrutiny of data that have potential public health implications is standard practice
- Initial review of results by EPA and other agencies suggested concentrations for the control group (South Carolina) were inconsistent with current scientific literature. Further investigation warranted.
- Search for effect levels to help interpretation of results

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Why are Metals Detected in Meconium?

- Most prenatal vitamins have copper, iron, zinc; some also contain chromium, manganese, molybdenum, selenium
- FDA Daily Values
  - Cu = 2 mg
  - Mn = 2 mg
  - Mo = 75 ug
  - Zn = 15 mg

➢ Detection of these beneficial minerals in meconium is expected

Supplement Facts

Serving size 3 Tablets
Servings per container 64

Amount per serving		%DV for adults	%DV for pregnant women
Vitamin A (100% as beta-carotene from ferment media)	1500 mcg	144%	100%
Vitamin C (as ascorbic acid from ferment media)	75 mg	83%	63%
Vitamin D3 (as cholecalciferol from ferment media)	25 mcg (1000 IU)	125%	167%
Vitamin E (as d-alpha-tocopheryl acetate from ferment media)	20.9 mg	139%	110%
Vitamin K (as phylloquinone [K1] from ferment media and as menaquinone-7 [K2] from natto)	90 mcg	75%	98%
Thiamin (as thiamine hydrochloride from ferment media)	1.4 mg	117%	100%
Riboflavin (from ferment media)	1.6 mg	123%	100%
Niacin (as niacinamide from ferment media)	18 mg	113%	100%
Vitamin B6 (as pyridoxine hydrochloride from ferment media)	5 mg	294%	250%
Folate (as methylfolate, and as 105 mcg folic acid from ferment media)	600 mcg DFE	150%	100%
Vitamin B12 (as cyanocobalamin from ferment media)	3 mcg	125%	107%
Biotin (from ferment media)	35 mcg	117%	100%
Pantothenic Acid	7 mg	140%	100%
Calcium (from algae *Lithothamnion* [*Lithothamnion calcareum* and *Lithothamnion corallioides*])	75 mg	6%	6%
Iron (as ferrous fumarate from ferment media)	27 mg	150%	100%
Iodine (as potassium iodide from ferment media)	150 mcg	100%	52%
Magnesium (as magnesium oxide from ferment media and algae *Lithothamnion* [*Lithothamnion calcareum* and *Lithothamnion corallioides*])	15 mg	4%	4%
Zinc (as zinc oxide from ferment media)	6.5 mg	59%	50%
Selenium (as selenium dioxide from ferment media)	70 mcg	127%	100%
Copper (as copper sulfate anhydrous from ferment media)	0.65 mg	72%	50%
Manganese (as manganese chloride from ferment media)	2.6 mg	113%	100%
Chromium (as chromium chloride from ferment media)	45 mcg	129%	100%
Molybdenum (as sodium molybdate from ferment media)	20 mcg	44%	40%

CODE 286412 KOG

Directions: As a dietary supplement, take two caplets daily with food.

Supplement Facts

Serving Size Two Caplets
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin A (as beta-Carotene)	4500 IU	90%
Vitamin C (as Ascorbic Acid)	120 mg	200%
Vitamin D (as Cholecalciferol D-3)	400 IU	100%
Vitamin E (as Natural d-alpha Tocopheryl Succinate)	30 IU	100%
Thiamin (Vitamin B-1)(as Thiamin Mononitrate)	1.4 mg	93%
Riboflavin (Vitamin B-2)	1.6 mg	80%
Niacin (as Niacinamide)	18 mg	90%
Vitamin B-6 (as Pyridoxine Hydrochloride)	8 mg	400%
Folic Acid	1000 mcg	125%
Vitamin B-12 (as Cyanocobalamin)	6 mcg	100%
Biotin	35 mcg	12%
Calcium (as Calcium Carbonate)	600 mg	46%
Iodine (as Potassium Iodide)	200 mcg	133%
Magnesium (as Magnesium Oxide)	200 mg	54%
Zinc (as Zinc Oxide)	15 mg	100%
Copper (as Copper Gluconate)	1.3 mg	65%
Selenium (as Selenium Yeast)	70 mcg	*
Manganese (as Manganese Sulfate)	2.6 mg	*
Chromium (as Chromium Yeast)	45 mcg	*
Molybdenum (as Sodium Molybdate)	50 mcg	*
Boron (as Boron Citrate)	150 mcg	*
Choline (as Choline Bitartrate)	350 mg	*

‡ Daily Value for pregnant or lactating women.
* Daily Value not established.

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Manganese

- An essential mineral nutrient needed for proper **fetal development** and other important aspects of metabolism.
- Excess manganese during the second trimester may increase risk for preterm delivery
- Findings of two recent studies indicate that lower maternal blood manganese is associated with fetal intrauterine growth retardation (IUGR) and lower birth weight.

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Copper

- Copper is an essential micronutrient
- Elevations of copper in pregnancy is exceedingly rare, it is treated the same as Wilson's disease. The goal is to prevent fetal growth restricting and neurological sequelae in the newborn and preeclampsia in the mother.
- Deficiencies during pregnancy and development can lead to serious consequences, both short and long-term.

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Zinc

- A mineral micronutrient that plays an essential role in fetal development.
- Prenatal zinc supplementation leads to a statistically significant lower incidence of preterm birth.
- Maternal zinc deficiency during pregnancy is linked with adverse pregnant outcomes including abortion, preterm delivery, stillbirth and fetal neural tube defects.

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What else can influence metal concentrations in newborns?

- Based on meconium metal concentrations
  - Gestational age (24-28 weeks vs. 38-42 weeks)
    - Cu: 1.3x decrease
    - Mn: 3.8x increase
    - Zn: 2.3x increase
  - Birth Weight (<1,500 g vs. >2,500 g)

- Based on blood metal concentrations
  - Nutritional status
  - Maternal age
  - Infant gender
  - Maternal smoking status
  - Season of sample collection
  - Maternal pre-pregnancy BMI
  - Maternal education level

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Current Literature on Meconium Metal Concentrations

- EPA compiled meconium data in the scientific literature from 17 studies spanning more than 50 years

- This compilation includes all three citations noted in the McDermott paper
  - Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) Study (n= 1,591 meconium samples) – Arbuckle et al. (2016)/Ettinger et al. (2017)
  - Aziz et al. (2017), Pakistan study (n = 302)
  - Turker et al. (2013), Turkey study (n=291)

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What is the MIREC Study?

Maternal-Infant Research on Environmental Chemicals (MIREC) Study

- National, multi-year, research study (~2,000 participants).
- Began in 2007 and includes 10 cities across Canada.
- MIREC study provides a snapshot of typical metal levels in meconium.

Study Goals:

- Measure the extent to which pregnant women and their babies are exposed to environmental chemicals, as well as tobacco smoke.
- Assess what health risks, if any, are linked to exposure to increased levels of environmental chemicals.
- Measure the levels of environmental chemicals and nutritional factors in human milk.
- Collect small amounts of body fluids from consenting participants to store in the MIREC biobank for further research.

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McDermott Study, Table 1 – Meconium Metal Conc.

	Butte, MT N = 15	Columbia, SC N = 17	Wilcoxon rank sum test p-Value	*t*-Test p-Value
	Units: μg kg^{-1} Median (minimum, maximum) Mean (standard deviation)			
As	Median 32 Min 16, Max 49 Mean 35 Std Dev. 10	<LoD <LoD	<0.0001	<0.0001
Cu	Median 26,311 Min 11,006, Max 47,270 Mean 28,134 Std Dev. 10,411	Median 14.68 Min 2.40, Max 27.42 Mean 14.75 Std Dev. 7.68	<0.0001	<0.0001
Mn	Median 5364 Min 388, Max 18,120 Mean 6807 Std Dev. 5726	Median 3.25 Min 0.20, Max 12.83 Mean 4.67 Std Dev. 4.48	<0.0001	<0.0001
Mo	Median 59 Min 24, Max 105 Mean 64 Std Dev. 22	<LoD <LoD	<0.0018	<0.0018
Pb	Median # Mean 5 Std Dev. 5	<LoD <LoD	<0.0001	<0.0001
Zn	Median 81,642 Min 22,120, Max 312,695 Mean 109,154 Std Dev. 82,772	Median 43.34 Min 12.17, Max 117.25 Mean 53.74 Std Dev. 36.16	<0.0001	<0.0001

Limits of Detection (LoD) for MT samples:
As = 5.0, Cu = 5.0, Mn = 5.0, Mo = 0.1, Pb = 0.1, Zn = 5.0
Limits of Detection (LoD) for SC samples:
As = 1.4, Cu = 0.5, Mn = 0.5, Mo = 0.7, Pb = 0.6, Zn = 1.8
#only one sample was above the limit of detection

- In most recent literature studies, meconium concentrations are reported as μg/g (ppm) and not μg/kg (ppb)

Concentration values converted to μg/g (ppm)

Metal	Butte, MT	Columbia, SC
As	Median: 0.032 Mean: 0.035	Median: <LOD Mean: <LOD
Cu	Median: 26.311 Mean: 28.134	Median: 0.01468 Mean: 0.01475
Mn	Median: 5.364 Mean: 6.807	Median: 0.00325 Mean: 0.00467
Mo	Median: 0.059 Mean: 0.064	Median: <LOD Mean: <LOD
Pb	Median: NC Mean: 0.005	Median: <LOD Mean: <LOD
Zn	Median: 81.642 Mean: 109.154	Median: 0.04334 Mean: 0.05374

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Conversions and Assumptions

- Literature meconium concentration values usually expressed as dry weight
  - Authors indicated McDermott study values are presented as "as received"
- Meconium moisture content is 70-75% (per Harries 1978)
  - DW = WW / Fraction Solids
  - McDermott study values would be about 3-4 times higher if converted to dry weight
  - McDermott et al. concentrations adjusted from wet weight to dry weight assuming a moisture content of 70% [dw = ww / (1 - 0.7)]
- Results reported in terms of infant body weight; adjusted based on the median body weight 2.070 kg (Turker 2013)
- Results reported in terms of total metal (expressed as concentration assuming the mean reported mass of stool 8.9 g (Friel 1989)

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Results Comparison

Metal	Meconium Concentration (µg/g)													
	McDermott et al. (2019) [a]				Cassoulet et al. 2019*		MIREC (Arbuckle et al. 2016/ Ettinger et al. 2017)*			Aziz et al. 2017	Peng et al. 2015	Hamzaoglu 2014	Turker et al. 2013	Yang et al. 2013
	n=15		*n=17*		*n=371*		*n=1,591*			*n=309*	*n=190*	*n=18*	*n=304*	*n=102*
	Butte, MT Median		Columbia, SC Median		Median	Range	Median	95th %tile	Maximum	Mean Range by Location (dry wt.)	Control, Median (dry wt.)	Non-industrial district, Median	Surviving, Median [c]	Range
	as wet weight	as dry weight [b]	as wet weight	as dry weight [b]										
Arsenic	0.032	0.11	<LOD	<LOD	0.123	ND - 0.72	NC	0.02	0.55	---	0.03778	0.07	---	[e]
Copper	26.311	88	0.01468	0.049	67.18	15 - 250	---	---	---	1.6 - 28.7	---	67.05	99.77	---
Manganese	5.364	18	0.00325	0.011	14.31	1 - 100	4.9	15	40	---	---	---	---	---
Molybdenum	0.059	0.20	<LOD	<LOD	---	---	---	---	---	---	---	---	---	---
Lead	NC (0.005+)	NC (0.017+)	<LOD	<LOD	0.022	ND - 0.35	NC	0.0085	0.48	1.2 - 14.4	0.13568	0.041	30.84	[e]
Zinc	81.642	272	0.04334	0.14	313.8	20 - 1,500	---	---	---	9.5 - 160.3	---	244.5	190.44	---

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Results Comparison (cont.)

Metal	Meconium Concentration (µg/g)										
	Vall et al. 2012		**Turker et al. 2006**	**Lall et al. 2005**	**Ostrea et al. 2002**	**Golamco et al. (2000)**	**Haram-Mourabet 1998**	**Gonzalez de Dios 1996**	**Baranowski 1996**	**Friel 1989**	**Kopito 1966**
	n=37		*n=117*	*n=15*	*n=426*	*n=26*	*n=34*	*n=38*	*n=26*	*n=27*	*n=65*
	Median (dry wt.)	95th %tile (dry wt.)	Median	AGA Newborns, Mean (dry wt.)	Median	Range of means, >36wks (dry wt.)	Mean Range by Gestational Age	Full-term, Mean (Table III)	Control Mean	Mean, full-term [d]	Control Mean
Arsenic	0.0056	0.0255	---	---	<LOD	---	---	---	---	---	---
Copper	---	---	116.8	115.8	---	79.7 - 93.6	90.3 - 154.2	36.4	15.2	27.5	64
Manganese	---	---	---	40.2	---	24.7 - 25.4	9.5 - 35.8	4.1	---	7.0	20
Molybdenum	---	---	---	---	---	---	---	0.145	---	---	---
Lead	---	---	46.5	---	[f]	---	---	0.289	0.0047	---	---
Zinc	---	---	234	482.8	---	456.1 - 667.7	156.4 - 365.4	76	68	107.5	230

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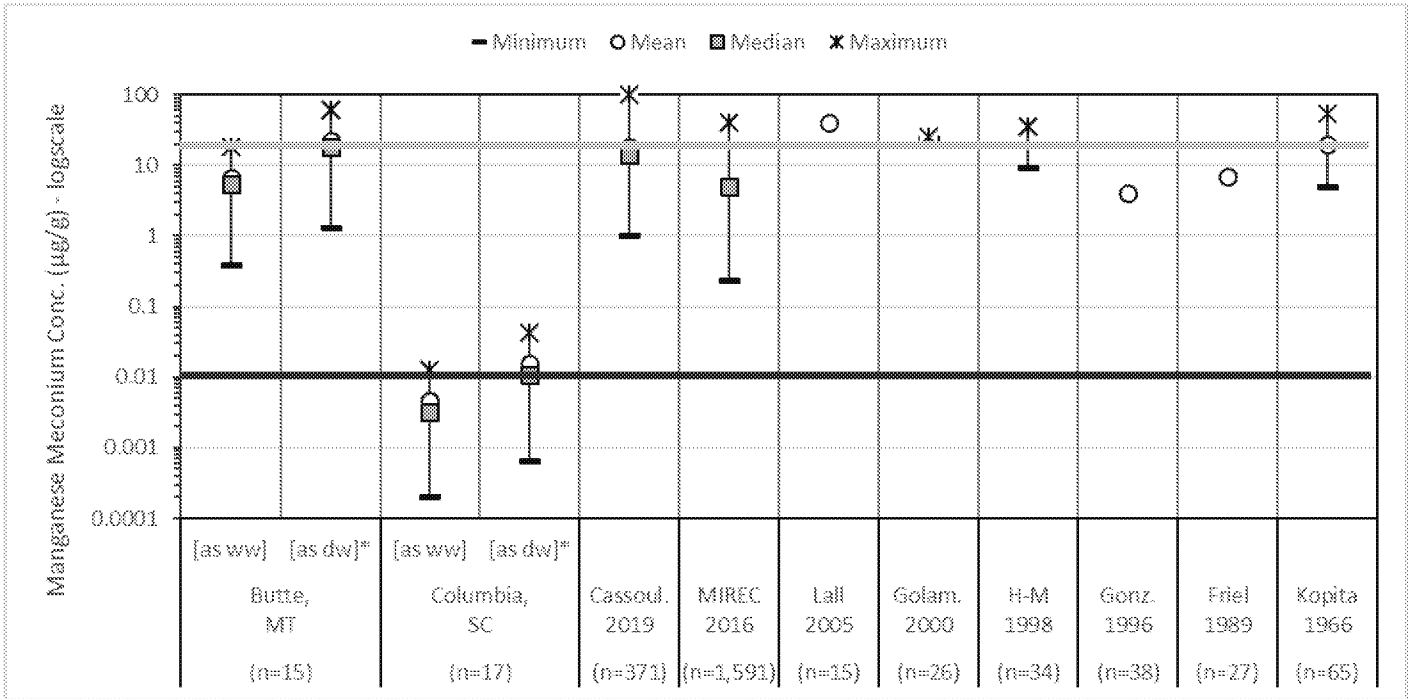
Results Comparison - Manganese



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Results Comparison – Manganese (cont.)

- McDermott Table 1 Median Concentrations
  - Manganese example *[Median; Min – Max]*
    - Butte = 5.364; 0.388 – 18.120 µg/g dry weight
    - Columbia = 0.00325; 0.0002 – 0.01283 µg/g dry weight
    - MIREC = 4.9; 0.24 – 40 µg/g dry weight
  - Comparison to other meconium datasets shows…
    - Butte concentrations are within the range of observed literature concentrations
    - Columbia concentrations are more than 1,000x lower than observed literature concentrations

➢ Columbia, SC results much lower than either Butte or other studies in the literature

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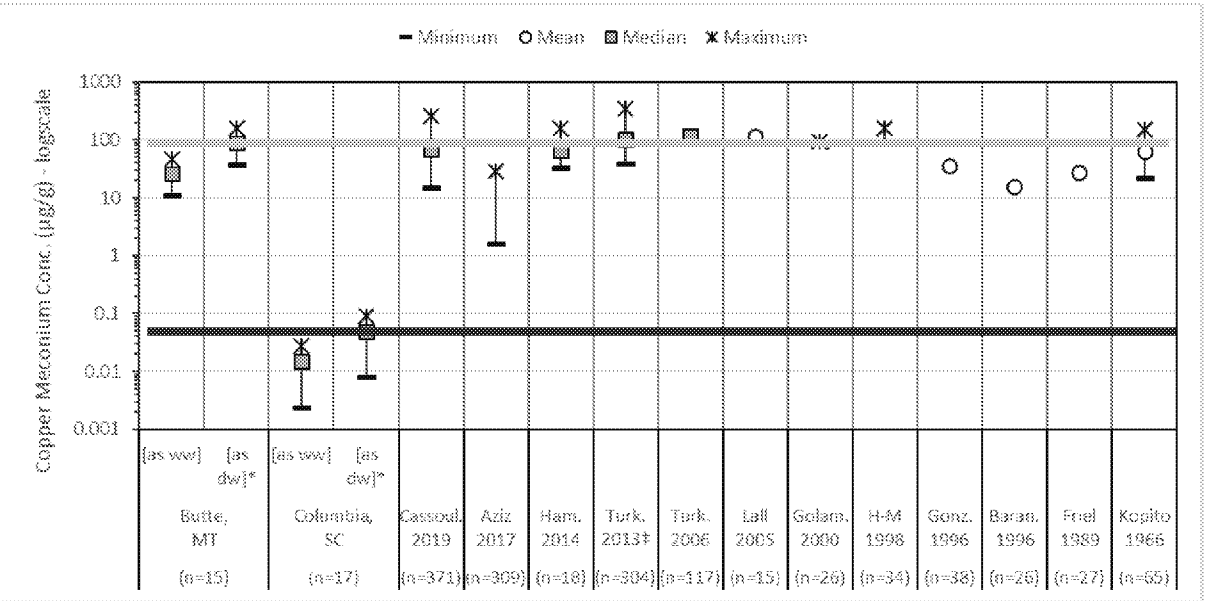
Results Comparison - Copper



Butte mean = 28.134 µg/g dry wt.

Columbia mean = 0.01475 µg/g dry wt.

- Comparison to other studies shows…
  - Butte concentrations are similar to other study concentrations
  - Columbia concentrations are more than 1,000x lower than other study concentrations

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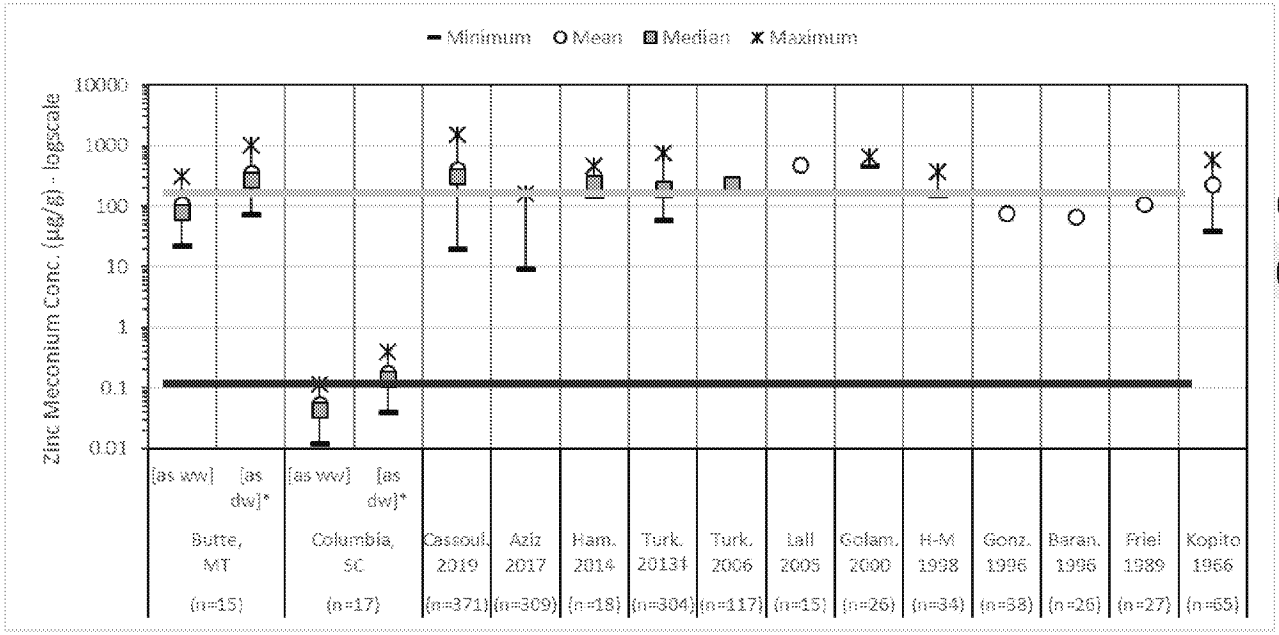
Results Comparison - Zinc



Butte = 109.154 µg/g dry wt.

Columbia = 0.05374 µg/g dry wt.

- Comparison to other studies shows…
  - Butte concentrations are similar to other study concentrations
  - Columbia concentrations are more than 1,000x lower than other study concentrations

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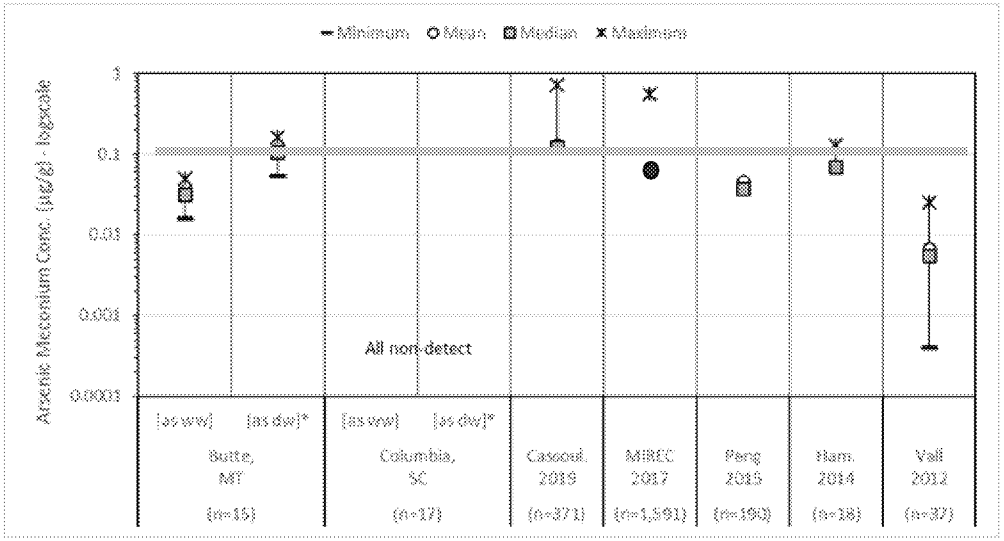
Results Comparison - Arsenic

- McDermott *[median, min-max]*
  - Butte: 0.032; 0.016 – 0.049 µg/g dry wt.
  - Columbia: all <LOD
- MIREC *[median, 95th %tile, max]*
  - NC, 0.02, 0.55 µg/g dry wt.
    - NC = not calculated due to low detection frequency



➢ Butte concentrations are within the range of observed MIREC concentrations and consistent with other studies in the literature

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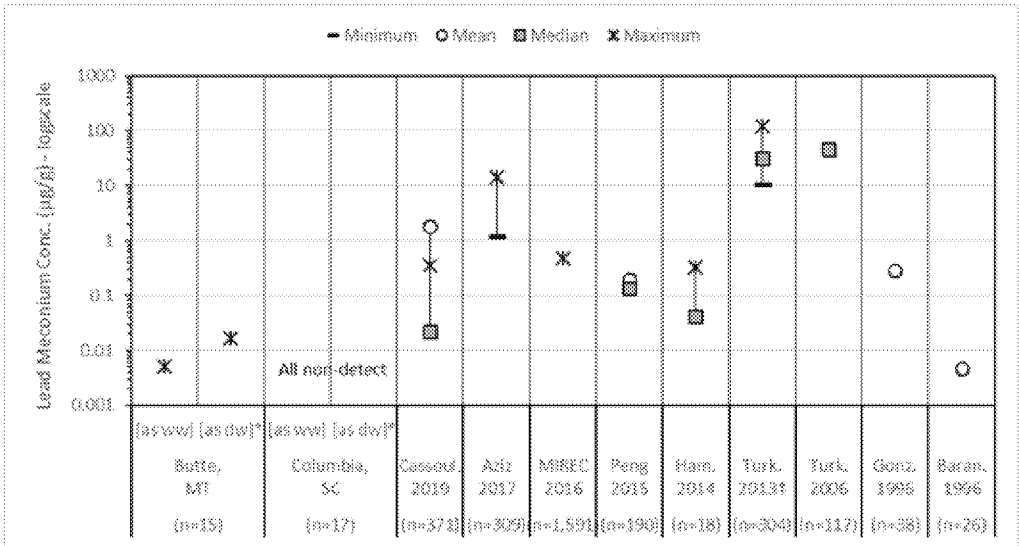
Results Comparison - Lead

- McDermott
  - Butte: single detect of 0.005 µg/g dry wt.
  - Columbia: all <LOD
- MIREC *[median, 95th %tile, max]*
  - NC, 0.0085, 0.48 µg/g dry wt.
    - NC = not calculated due to low detection frequency



➢ Butte concentrations are within the range of observed MIREC concentrations and lower than other studies in the literature

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EPA requested additional information from McDermott et al.

- EPA requested the laboratory output for both the Butte and Columbia meconium datasets to allow for a review of the original, unprocessed data.
- Butte shared their laboratory output.
- EPA requested the archived meconium samples for both Butte and Columbia for possible reanalysis.

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EPA Interpretation of Meconium Metal Concentrations

- No established reference levels for metals in meconium
- Currently no available data to establish health effects/toxicity relationships
- Butte, MT meconium metals concentrations appear to be within the observed range based on scientific literature
  - Arsenic and lead concentrations are similar to MIREC study
  - Only one lead detection; indicates infants in Butte are similar to those in the general population, consistent with the current Superfund Health Study conclusions
- Columbia, SC meconium metal concentrations appear uncharacteristically low based on scientific literature

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Other Reviews of McDermott et al. 2019

- ATSDR issued a letter to BSB and Montana DPHHS (12/13/2019)
- DPHHS conducting a Letter Health Consult under the ATSDR CO-OP program (due in Feb)
- Montana Resources hired subject matter experts and conducted an independent review and wrote an external memorandum
- DPHHS performed a cursory evaluation of laboratory quality control information for the Butte results (Montana Environmental Laboratory, Public Health and Safety Division)

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Questions?

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